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HORMONE COMPOSITION

The present invention relates to a composition containing oestrogen, which is to be administered vaginally.

BACKGROUND OF THIS INVENTION

Vaginal atrophy can occur in postmenopausal woman and estrogen deprived women who actually do not need any systemic hormone replacement therapy but just local therapy. Consequently, local, topical treatment is preferred in order to avoid the systemic side effects due to long-lasting oestrogen therapy. Local therapy for this purpose has been studied for a long period of time and the hormone has been administered as creams, gels, and silastic rings.

About every second postmenopausal women will experience urogenital discomfort associated with estrogen deficiency. Previous studies have shown that although many of these women use an oral hormone replacement therapy, urogenital symptoms persist.

A composition commonly used is Vagifem® marketed by Novo Nordisk A/S. Vagifem is developed to treat estrogen deficiency-deprived atrophic vaginitis. Vagifem is a small tablet containing 25 μg 17β-estradiol. A usual treatment is one tablet daily for the first 2 weeks of-treatment and, thereafter, one tablet twice a week. Conveniently, Vagifem is administered by placing a tablet at the top of a slim-line pencil-like disposable applicator. By introducing the applicator to the vagina, the Vagifem tablet will, due to the adhesive characteristics of Vagifem, stay in the vagina.

SUMMARY OF THIS INVENTION

One object of this invention is to furnish a hormone composition which gives a clinical effect on vaginal symptoms which is as good as that obtained by administration of Vagifem twice weekly.

A further object of this invention is to furnish a hormone composition furnishing no or only inferior systemic absorption.

A still further object of this invention is to furnish a hormone composition furnishing significant improvement in the vaginal mucosa.

A still further object of this invention is to furnish a hormone composition furnishing no or only inferior systemic effect.

A still further object of this invention is to furnish a hormone composition furnishing low absorption of estrogen.

A still further object of this invention is to furnish a hormone composition furnishing low serum concentration of estradiol.

A still further object of this invention is to furnish a hormone composition furnishing no or only inferior accumulation of circulating estradiol.

A still further object of this invention is to furnish a hormone composition furnishing positive effects on an atrophic vaginal epithelum.

A still further object of this invention is to furnish a hormone composition furnishing complete or substantial vaginal maturation.

A still further object of this invention is to furnish a hormone composition furnishing a reduced risk of osteporosis.

A still further object of this invention is to furnish a hormone composition furnishing increases in percentage of superficial vaginal cells.

A still further object of this invention is to furnish a hormone composition which can be used for the treatment of atrophic vaginitis.

A very specific object of this invention is to furnish a hormone composition furnishing all or most of the following characteristics: Relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and improved cytologic maturation of both the vaginal and urethral mucosa.

DETAILED DESCRIPTION OF THIS INVENTION

The vaginal symptoms treated by the use according to the present invention are dryness, soreness, irritation, and dyspareunia. The urogenital health is characterized by secretions, epithelial integrity, surface thickness, and the pH value of the vagina.

Surprisingly, it has been found that the use according to the claims below have pharmaceutical and clinical advantages compared with the known uses of similar compositions.

It is often recommended to proceed the use according to the claims below with a treatment with a somewhat higher dosage of an estrogen, for example, estradiol. Such a treatment is

herein designated a pre-treatment. In a preferred embodiment, this pre-treatment is the daily treatment with the same dose as that used for a bi-weekly use according to the claims below.

The compositions used according to this invention may be prepared analogously to the preparation of similar compositions, for example, Vagifem. The compositions used according to this invention may contain any constituent used or suggest to be used in similar compositions. The compositions used according to this invention may be administered analogously with the administration of similar compositions. All these aspects are known to the skilled art worker.

The present invention is further illustrated by the following example which, however, is not to be construed as limiting the scope of protection. Also, the present invention is further illustrated at pages 1-29 below being a part of this description. These additional pages are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description, in the following examples and at pages 1-29 below may, in any combination thereof, be material for realising the invention in diverse forms thereof.

Example 1

58 postmenopausal women were treated with tablets containing either 10 or 25 μg 17β-estradiol. The women inserted 1 tablet intravaginally, once daily for the initial 2 weeks of the study and then twice per week (Sunday & Thursday) for the following 10 weeks. Hence, some of the women only received tablets containing 10 μg 17β-estradiol and the remaining women only received tablets containing 25 μg 17β-estradiol. The estradiol profile when administering 25 or 10 μg 17β-estradiol was similar after the first dose (zero weeks of treatment) and after the above continuous treatment with 25 or 10 μg 17β-estradiol twice weekly for 10 weeks.

CLAIMS

1. The use of an oestrogen in the manufacture of a composition containing oestrogen for the treatment of atrophic vaginitis in woman, by administering weekly an amount of about 10 to about 30 μg estradiol to a woman.

2. The use according to claim 1, wherein the women treated are menopausal or post-menopausal women.

3. The use according to any one of the preceding claims, wherein the weekly amount of about 15 to about 25 μg estradiol.

4. The use according to any one of the preceding claims, wherein daily about 1.5 to about 4 μg estradiol is administered.

5. The use according to any one of the preceding claims, wherein daily about 2 to about 3 μg estradiol is administered.

6. The use according to any one of the preceding claims, wherein twice weekly about 5 to about 15 μg estradiol is administered.

7. The use according to any one of the preceding claims, wherein twice weekly about 7 to about 13 μg estradiol is administered.

8. The use according to the preceding claim, wherein twice weekly about 9 to about 11 μg estradiol is administered.

9. The use according to any one of the preceding claims, wherein no progestogen is administered.

10. The use according to any one of the preceding claims, wherein the composition is to be administered vaginally.

11. The use according to any one of the preceding claims, wherein it is used for a period of time of more than 2 weeks, preferably more than 1 month, more preferred more than 2 months, and even more preferred more than 3 months.

12. A method of treating atrophic vaginitis, comprising administering a composition as described in any of the previous use claims.

13. Any novel feature or combination of features described herein.

Novo Nordisk A/S

17 β-Estradiol Vaginal Tablets Versus Placebo for Treatment of Atrophic Vaginitis

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Key words: Vaginal tablets, Atrophic vaginitis, Menopause, Estrogen replacement therapy

Running foot: 17 β-estradiol vaginal tablets

PRECIS

Treatment with low-dose 17 β-estradiol vaginal tablets relieves vaginal symptoms, improves urogenital atrophy, and increases maturation of the vaginal and urethral epithelia.

ABSTRACT

Objectives: Vaginal tablets containing 25 μg 17 β-estradiol (E2), 10 μg 17 β-E2, or placebo were evaluated for efficacy and safety in postmenopausal women with atrophic vaginitis.

Methods: In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, 230 postmenopausal women received treatment with 25 μg 17 β-E2, 10 μg 17 β-E2, or placebo for 12 weeks. Efficacy was measured with composite scores of vaginal symptoms (dryness, soreness, and irritation) and urogenital health (secretions, epithelial integrity, surface thickness, and pH). Vaginal and urethral cytology analyses for maturation were also performed. Safety assessments included a post-treatment endometrial biopsy.

Results: Greater improvements in composite scores for patient-reported vaginal symptoms and investigator-reported urogenital health characteristics at Weeks 2, 7, and 12 were reported in the active treatment groups than in the placebo group. Significantly greater improvements were reported at Weeks 7 and 12 ($P \leq .05$). At Week 12, over 75% of subjects in the active treatment groups had vaginal pH values below 5.5 compared to approximately 40% of subjects in the placebo group. Both vaginal and urethral cytology analyses indicated statistically significant increases or trends toward increases in percentage of superficial cells in the active treatment groups than in the placebo group ($P \leq .05$). One subject who received 25 μg 17 β-E2 had hyperplasia on endometrial biopsy at Week 12.

Conclusions: The 17 β-E2 vaginal tablets provided relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and improved cytologic maturation of both the vaginal and urethral mucosa.

INTRODUCTION

As endogenous estrogen production declines during menopause, the vagina and other estrogen-dependent tissues gradually undergo atrophic changes. The loss of estrogen-dependent cellular maturation to the vagina results in atrophic vaginitis, with symptoms of dryness, soreness, irritation, discharge, and dyspareunia. Additionally, the vaginal epithelium becomes more susceptible to infection and secondary inflammation.

Although postmenopausal atrophic vaginitis is a common condition in elderly women, only a small percentage of those affected receive treatment with estrogens.[1,2,3] In symptomatic women who have no other indications for systemic hormone replacement or prefer not to use systemic therapy, local vaginal treatment with estrogen is effective in reversing atrophic vaginal changes and relieving symptoms.

Several studies have examined the intravaginal administration of micronized estradiol (E2) and conjugated equine estrogens with doses that ranged between 0.3 and 2.5 mg per day and have shown that systemic absorption of estrogen results.[4,5,6,7,8] The doses used in these studies ranged between 0.3 and 2.5 mg per day, which result in systemic absorption of estrogen. A newly developed low-dose estrogen vaginal tablet that contains 25 μg 17 β-E2 in a hydrophilic cellulose-based matrix has been shown to promote steady absorption in an atrophic vaginal vault, with absorption significantly reduced after maturation of the epithelium.[9] The innovative use of a vaginal tablet to deliver 17 β-E2 to the vaginal epithelium assures administration of a consistent dose of estrogen to the epithelial tissue, eliminates the staining of adjoining tissues or undergarments often associated with vaginal creams, and relieves atrophic vaginitis symptoms without the need for daily treatment.[10]

This study evaluated and compared the efficacy and safety of vaginal tablets containing 25 μg 17 β-E2, 10 μg 17 β-E2, or placebo during 12 weeks of therapy for vaginal atrophy in menopausal women.

METHODS AND MATERIALS

This phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 9 centers in the United States. The study was approved by the appropriate institutional review boards, and informed consent was obtained from each subject prior to beginning study procedures. The study was conducted in compliance with the Declaration of Helsinki of 1975, revised in 1983.

Women at least 45 years of age or older with moderate-to-severe vaginal dryness and soreness were enrolled. All subjects were required to have serum E2 concentrations of 20 pg/mL or less and to have no more than 5% superficial vaginal cells. Subjects with intact uteri were also required to be at least 12 months past natural menopause with an endometrial thickness of 5 mm or less, as determined by pelvic sonogram. Subjects did not undergo a prestudy endometrial biopsy.

Subjects with creatinine levels greater than 1.4 mg/dL, bilirubin levels greater than 1.2 mg/dL, aspartate transaminase levels greater than 50 U/L, or hemoglobin levels less than 11.5 g/dL were excluded from the study. Known or suspected history of breast carcinoma, hormone-dependent tumor, genital bleeding of unknown etiology, acute thrombophlebitis or thromboembolic disorder associated with estrogen use, vaginal infection requiring treatment, allergy to the test drug or its constituents, or any serious disease or chronic condition that could interfere with study compliance were study exclusions. The use of an investigational drug within the 30 days preceding screening, any homeopathic preparation within the 7 days preceding study drug

initiation, any exogenous corticosteroid or sex hormones within the 8 weeks preceding study drug initiation, or diethylstilbestrol was prohibited.

The purpose of this study was to compare vaginal tablets containing 25 μg 17 β-E2 with placebo in a US population. At the time of this study, this vaginal tablet was in use in XX other countries. This study also included a third treatment arm for vaginal tablets containing 10 μg 17 β-E2. The 10-μg 17 β-E2 tablet may be developed for over-the-counter use. Using a computer-generated randomization scheme, subjects were randomized using a 2:2:1 ratio to receive vaginal tablets that contained 25 μg 17 β-E2, 10 μg 17 β-E2, or placebo. All vaginal tablets were identical in appearance. Subjects inserted vaginally 1 tablet daily for 14 days and then 1 tablet twice per week (Sunday and Thursday) for the remainder of the trial. Subjects were to insert the tablets at the same time each day (preferably at bedtime). Subjects were evaluated for efficacy and safety at Weeks 2, 7, and 12.

Efficacy assessments included subject ratings of atrophic vaginitis symptoms, investigator ratings of urogenital health including vaginal pH, and vaginal and urethral cytology. Subjects used intensity ratings of none, mild, moderate, or severe to evaluate atrophic vaginitis symptoms (dryness, soreness, irritation, dyspareunia, and vaginal discharge). Intensity ratings were assigned ascending scores from 0 (none) to 3 (severe) for analysis. Investigators used the same severity scale of none, mild, moderate, or severe atrophy to record vaginal health characteristics (secretions, epithelial integrity, surface thickness, color, and pH). Severity categories were assigned ascending scores from 0 (none) to 3 (severe) for analysis.

To avoid multiple endpoint issues, composite scores were defined. A composite score for atrophic vaginitis symptoms was defined as the average of the individual symptom scores for dryness, soreness, and irritation. This composite score did not include scores for dyspareunia,

which was not evaluated by every subject, or vaginal discharge, which was rated as none or mild by the majority of subjects. A composite score for urogenital health was defined as the average of the individual urogenital health characteristic scores. A test of linear association between symptoms or characteristics was performed within each treatment group using data for the change from baseline in individual symptom or characteristic scores at Week 7. The Spearman rank correlation coefficients between each pair of symptoms or characteristics ranged between .295 and .504. Although the magnitude of the correlation was not strong due to the nature of categorical data, each pair of symptoms or characteristics was positively linearly associated (significantly; $P \leq .001$). Therefore, the composite scores provided reasonable overall evaluations of the treatment effect in relieving atrophic vaginitis. The composite scores and the changes from baseline for the composite scores were examined at each time point.

Vaginal and urethral cell samples were harvested by the investigators and analyzed by independent cytologists to determine the percentages of parabasal, intermediate, and superficial cells. For composite scores, and vaginal and urethral cell samples, differences within and between treatment groups were analyzed using an analysis of variance (ANOVA).

Endometrial biopsies were performed at the end of the study in subjects with intact uteri. The number of subjects with abnormal biopsies was compared between treatment groups.

RESULTS

A total of 91 women received 25 μg 17 β-E2, 92 women received 10 μg 17 β-E2, and 47 women received placebo. Demographic and baseline characteristics did not differ significantly between treatment groups, with the exception of race (Table 1). The percentage of nonwhite subjects was significantly lower in the 25-μg 17 β-E2 group than in the placebo group ($P = .026$, Cochran-Mantel-Haenszel test). **[PLEASE CONFIRM: No comparisons of demographic information**

with the 10-μg 17 β-E2 group.] Nine subjects (9.9%) in the 25-μg 17 β-E2 group and 8 subjects (17.0%) in the placebo group did not complete the study. The most common reasons for study discontinuation were adverse events and protocol noncompliance.

The vaginal symptom composite score profiles between Weeks 0 and 12 are presented in Figure 1. At Week 0, the vaginal symptom composite scores measured approximately 1.9 in each treatment group. At Weeks 2, 7, and 12, vaginal symptom composite scores were significantly lower than the corresponding baseline values for each treatment group ($P \leq .001$; two-tailed paired t-test). In the active treatment groups (the 25- and 10-μg 17 β-E2 groups), vaginal symptom composite scores continued to decrease after Week 0 and measured approximately 0.5 and 0.6 at Week 12, respectively. In contrast, in the placebo group, vaginal symptom scores remained nearly constant after Week 0 and measured approximately 1.1. At Weeks 7 and 12, the decreases from baseline observed in the active treatment groups were significantly larger than those observed in the placebo group ($P \leq .01$ and $P \leq .05$ in the 25- and 10-μg 17 β-E2 groups, respectively; two-tailed linear model analysis).

The urogenital health composite score profiles between Weeks 0 and 12 are presented in Figure 2. At Week 0, the urogenital health composite scores measured approximately 1.7 in each treatment group. At Weeks 2, 7, and 12, urogenital health composite scores were significantly lower than the corresponding baseline values for each treatment group ($P \leq .01$; two-tailed paired t-test). At Weeks 2, 7, and 12, the decreases in urogenital health composite scores observed in the active treatment groups were significantly larger than those observed in the placebo group ($P \leq .001$; two-tailed linear model analysis). At Week 7, the decrease in urogenital health composite score was significantly larger in the 25-μg 17 β-E2 group than in the 10-μg 17 β-E2 group ($P = .004$; two-tailed linear model analysis).

The number and percentage of subjects with vaginal pH values below 5.5 at Weeks 0, 2, 7, and 12 are presented in Table 2. At Week 0, approximately 35% of subjects in each treatment group had vaginal pH values below 5.5. At Weeks 2, 7, and 12, the percentage of subjects with vaginal pH values below 5.5 increased from the baseline percentages for each treatment group. These increases were significantly greater for subjects in the active treatment groups than in the placebo group ($P \leq .05$; two-tailed linear model analysis). At Week 12, over 75% of subjects in the active treatment groups and approximately 40% of subjects in the placebo group had vaginal pH values below 5.5.

The percentage of superficial cells from vaginal cytology analysis at Weeks 0, 2, 7, and 12 are presented in Figure 3. At all time points after Week 0, subjects in the active treatment groups showed either significant increases ($P \leq .05$) or trends toward increases in the percentage of superficial cells compared with subjects in the placebo group. These increases are presented in Table 4.

The percentage superficial cells from urethral cytology analysis at Weeks 0, 2, 7, and 12 are presented in Figure 5. At all time points after Week 0, subjects in the active treatment groups showed either significant increases ($P \leq .05$) or trends toward increases in the percentage of superficial cells compared with subjects in the placebo group. These increases are presented in Table 5.

The percentages of superficial vaginal and urethral cells at Weeks 0 and 12 are presented in Figures 6 (a), (b), and (c) for the 25- and 10-μg 17 β-E2 groups and the placebo group, respectively. At Week 0, the majority of subjects in each treatment group had percentages of both superficial vaginal and urethral cells less than or equal to 5% (57 subjects [81%], 53 subjects [85%], and 34 subjects [97%] in the 25- and 10-μg 17 β-E2 groups and the placebo

group, respectively). At Week 12, more subjects in the active treatment groups than in the placebo group had increases in percentages of both superficial vaginal and urethral cells (52 subjects [74%], 44 subjects [71%], and 21 subjects [60%] in the 25- and 10-μg 17 β-E2 groups and the placebo group, respectively).

The endometrial biopsy results at Week 12 are presented in Table 3. Of subjects with biopsies that yielded sufficient tissue, 1 subject in the 25-μg 17 β-E2 group showed simple hyperplasia without atypia. However, there was no pretreatment biopsy for comparison.

DISCUSSION

Today, the life expectancy of women extends 30 years beyond the menopause.[2] An estimated 50% of postmenopausal women or more will experience some form of urogenital discomfort such as atrophic vaginitis.[11] Local therapies, such as the 17 β-E2 cellulose-based vaginal tablets used in this study, have been developed to relieve the symptoms of atrophic vaginitis without significant systemic absorption. This novel delivery system provides administration of a consistent dose of estrogen to the vaginal epithelium with twice-weekly maintenance dosing. In contrast, vaginal creams can be difficult for patients to measure, and patients often have trouble assuring that the entire dose is inserted into the vaginal vault. Vaginal creams may also cause staining of the vulva, peritoneum, and undergarments. Additionally, vaginal cream users often must alter timing of coitus for periods not immediately following vaginal cream application (typically at least 12 hours later).

In this 12-week study, treatment with 25- and 10-μg 17 β-E2 tablets resulted in greater improvement in vaginal symptoms (as assessed by the subjects) and urogenital health (as assessed by the investigators) than treatment with placebo. At each time point after baseline, improvements in the urogenital health composite scores were significantly greater in the active

treatment groups than in the placebo group ($P \leq .01$). At each time point after 2 weeks of treatment, improvements in the vaginal symptom composite scores were also significantly greater ($P \leq .05$). Additionally, subjects in the active treatment groups had statistically significant increases ($P \leq .05$) or trends toward increases in the percentage of superficial vaginal cells compared with subjects in the placebo group. In the active treatment groups, the percentage of superficial vaginal cells was highest after the 2-week period of daily dosing. Subsequently, during the maintenance period with twice-weekly dosing, the percentage of superficial vaginal cells began to decline, most likely as a result of the reduced weekly dose of 17 β-E2. However, at all time points after Week 0, the percentage of superficial vaginal cells remained higher than the baseline value.

Another clinical measure of vaginal atrophy is the vaginal pH, a component of the urogenital health composite score. As estrogen production declines after menopause, lactobacilli, which produce lactic acid from vaginal glycogen, disappear from the flora, and vaginal pH increases.[12] In this study approximately twice as many subjects who received 25 or 10 μg 17 β-E2 than those who received placebo had vaginal pH values below 5.5 after 12 weeks of treatment (75% versus 40%, respectively). The results from analysis of vaginal cytology and pH indicate a positive effect of the 25- and 10-μg 17 β-E2 vaginal tablets on estrogenation of the vaginal epithelium.

The lower portions of the vaginal and urinary tracts have the same embryological origin, and genital tract disorders such as atrophic vaginitis are often accompanied by atrophic changes in the urinary tract that may include dysuria, stress incontinence, and urinary tract infections.[1,9,12,13] Consequently, estrogen therapy may also have an effect on the urethral epithelium. In this study, the condition of the urethral epithelium was determined through urethral cytology. Similar to the vaginal epithelium, subjects in the active treatment groups had statistically significant increases

($P \leq .05$) or trends toward increases in the percentage of superficial urethral cells compared with subjects in the placebo group. Also similar to the superficial vaginal cells, the percentage of superficial urethral cells reached a maximum after 2 weeks of daily dosing and subsequently began to decline during the maintenance period (with twice-weekly dosing), most likely due to the reduced weekly dose of 17 β-E2. However, at all time points after Week 0, the percentage of superficial urethral cells remained higher than the baseline value.

In this study, higher percentages of superficial vaginal cells were usually associated with higher percentages of superficial urethral cells, and correspondingly, lower percentages of superficial vaginal cells were usually associated with lower percentages of superficial urethral cells. Vaginal cytology results appear to reflect urethral cytology results. Consequently, the results from vaginal cytology tests could be used as an indicator of urethral syndrome in women where this condition is suspected, avoiding the need for painful urethral testing.

Elevated systemic estrogen levels have been associated with endometrial hyperplasia or cancer.[14,15] In this study, after 12 weeks of treatment, 1 subject in the 25-μg 17 β-E2 group had simple hyperplasia without atypia. However, no prestudy endometrial biopsy was performed to assess the endometrial cavity prior to treatment. Another independent study using the same 25-μg 17 β-E2 tablets in 80 subjects reported no incidence of endometrial hyperplasia with endometrial sampling.[10]

This report presents data from a unique new cellulose-based matrix vaginal delivery system for 17 β-E2. In this dose-ranging study, both 25- and 10-μg 17 β-E2 vaginal tablets improved vaginal symptoms and urogenital health while delivering a fixed dose of 17 β-E2 to the vaginal epithelium. Also, the twice-weekly dosing regimen and the ease of application could encourage high treatment compliance for women who require long-term therapy for atrophic vaginitis.

These vaginal tablets would be a viable alternative for women who choose to use local versus systemic therapy to treat atrophic vaginitis.

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Table 1. Demographic and Baseline Characteristics

Characteristic	Treatment group: 25 μg 17 β-E2 (N = 91)	10 μg 17 β-E2 (N = 92)	Placebo (N = 47)
Age (yr)[a]	58.3 ± 7.4 (46-78)	57.7 ± 6.5 (46-79)	57.6 ± 4.8 (50-70)
Race			
White	88 (96.7%)	83 (90.2%)	41 (87.2%)
Nonwhite	3 (3.3%)[b]	9 (9.8%)	6 (12.8%)[b]
Time since last menses (yr)[a]	14.8 ± 9.6 (1-40)	13.5 ± 7.8 (1-34)	13.6 ± 8.1 (1-33)
Hysterectomized			
Yes	42 (46.2%)	44 (47.8%)	23 (48.9%)
No	49 (53.8%)	48 (52.2%)	24 (51.1%)

SD = standard deviation

[a] Mean ± SD (range)

[b] Statistically significant; $P = .026$ (Cochran-Mantel-Haenszel test)

[PLEASE CONFIRM: No comparisons of demographic information with the 10-μg 17 β-E2 group.]

Table 2. Number and Percentage of Subjects With Vaginal pH Values Below 5.5

	Treatment group					
	25 μg 17 β-E2		10 μg 17 β-E2		Placebo	
Time point	n/N	(%)	n/N	(%)	n/N	(%)
Week 0	31/90	(34.4)	27/89	(30.3)	17/46	(37.0)
Week 2	64/87	(73.6)[a]	67/84	(79.8)[b]	21/43	(48.8)
Week 7	71/83	(85.5)[b,c]	57/80	(71.3)[d]	23/44	(52.3)
Week 12	63/79	(79.7)[b]	54/71	(76.1)[b]	15/38	(39.5)

A two-tailed linear model analysis was used to compare treatment groups at each time point.

[a] Comparison with placebo, statistically significant; $P \leq .01$

[b] Comparison with placebo, statistically significant; $P \leq .001$

[c] Comparison with 10 μg 17 β-E2, statistically significant; $P \leq .05$

[d] Comparison with placebo, statistically significant; $P \leq .05$

Table 3. Endometrial Biopsy Results at Week 12

Result	Treatment group: 25 µg 17 β E2 (N = 32)	10 µg 17 β-E2 (N = 32)	Placebo (N = 21)
Normal[a]	28 (87.5%)	25 (78.1%)	18 (85.7%)
Abnormal[b]	1 (3.1%)	0 (0.0%)	0 (0.0%)
Other[c]	3 (9.4%)	7 (21.9%)	3 (14.3%)

[a] Results indicative of an atrophic endometrium, weakly proliferative endometrium, proliferative endometrium, or secretory endometrium were classified as normal.

[b] Results indicative of endometrial hyperplasia (simplex, complex, or atypical) or carcinoma were classified as abnormal.

[c] Results indicative of a menstrual endometrium, mucosal polyps, insufficient tissue, or other finding were classified as other.

Table 4. Mean and mean change from baseline in percentage of superficial vaginal cells

	Treatment group								
	25 μg 17 β-E2			10 μg 17 β-E2			Placebo		
Time point	N	Mean	Change	N	Mean	Change	N	Mean	Change
Week 0	86	4.0		79	3.1		45	4.3	
Week 2	85	34.2	30.7[a]	76	28.3	25.0[a]	42	13.1	8.6
Week 7	80	28.2	23.9[b,c]	72	20.4	17.1	41	15.1	10.4
Week 12	75	19.9	15.4	68	20.1	16.9[d]	36	13.8	9.0

A two-tailed linear model analysis was used to compare treatment groups at each time point.

[a] Comparison with placebo, statistically significant; $P \leq .001$

[b] Comparison with placebo, statistically significant; $P \leq .01$

[c] Comparison with 10 μg 17 β-E2, statistically significant; $P \leq .05$

[d] Comparison with placebo, statistically significant; $P \leq .05$

Table 5. Mean and mean change from baseline in percentage of superficial urethral cells

	Treatment group								
	25 μg 17 β-E2			10 μg 17 β-E2			Placebo		
Time point	N	Mean	Change	N	Mean	Change	N	Mean	Change
Week 0	86	3.2		83	2.5		42	3.0	
Week 2	83	21.9	19.2[a,b]	79	16.7	14.1[c]	34	6.5	3.3
Week 7	77	17.6	14.2[d]	70	13.5	10.7	38	8.6	5.5
Week 12	70	11.2	7.5	64	9.5	6.8	34	7.0	3.6

A two-tailed linear model analysis was used to compare treatment groups at each time point.

[a] Comparison with placebo, statistically significant; $P \leq .001$

[b] Comparison with 10 μg 17 β-E2, statistically significant; $P \leq .05$

[c] Comparison with placebo, statistically significant; $P \leq .01$

[d] Comparison with placebo, statistically significant; $P \leq .05$

Figure 1. Vaginal symptom composite score profiles – subjects who received at least 1 dose of study medication, had baseline assessments, and had at least 1 post-baseline assessment

—▲— 17-β E2 25 μg —□— 17-β E2 10 μg ---●--- Placebo

Figure 2. Urogenital health composite score profiles – subjects who received at least 1 dose of study medication, had baseline assessments, and had at least 1 post-baseline assessment

—▲— 17-β E2 25 μg —□— 17-β E2 10 μg ---●--- Placebo

Figure 3. Vaginal cytology results (percentage of superficial cells) – subjects who received at least 1 dose of study medication, had baseline assessments, and had at least 1 post-baseline assessment

■ 17-β E2 25 μg ▨ 17-β E2 10 μg □ Placebo

Figure 4. Maturation values – subjects who received at least 1 dose of study medication, had baseline assessments, and had at least 1 post-baseline assessment

—▲— 17-β E2 25 μg —□— 17-β E2 10 μg ---●--- Placebo

Figure 5. Urethral cytology results – subjects who received at least 1 dose of study medication, had baseline assessments, and had at least 1 post-baseline assessment

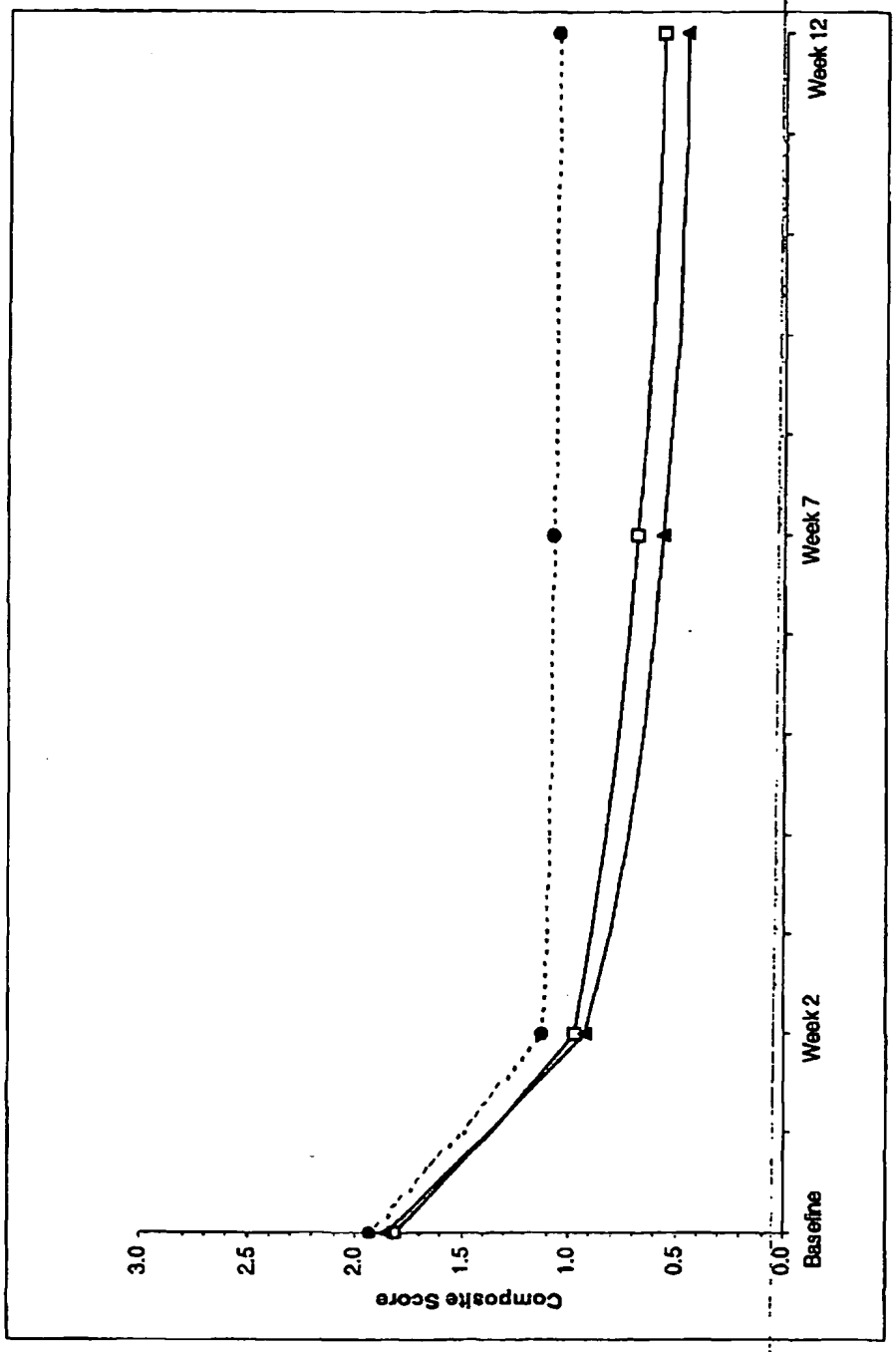
■ 17-β E2 25 μg ▨ 17-β E2 10 μg □ Placebo

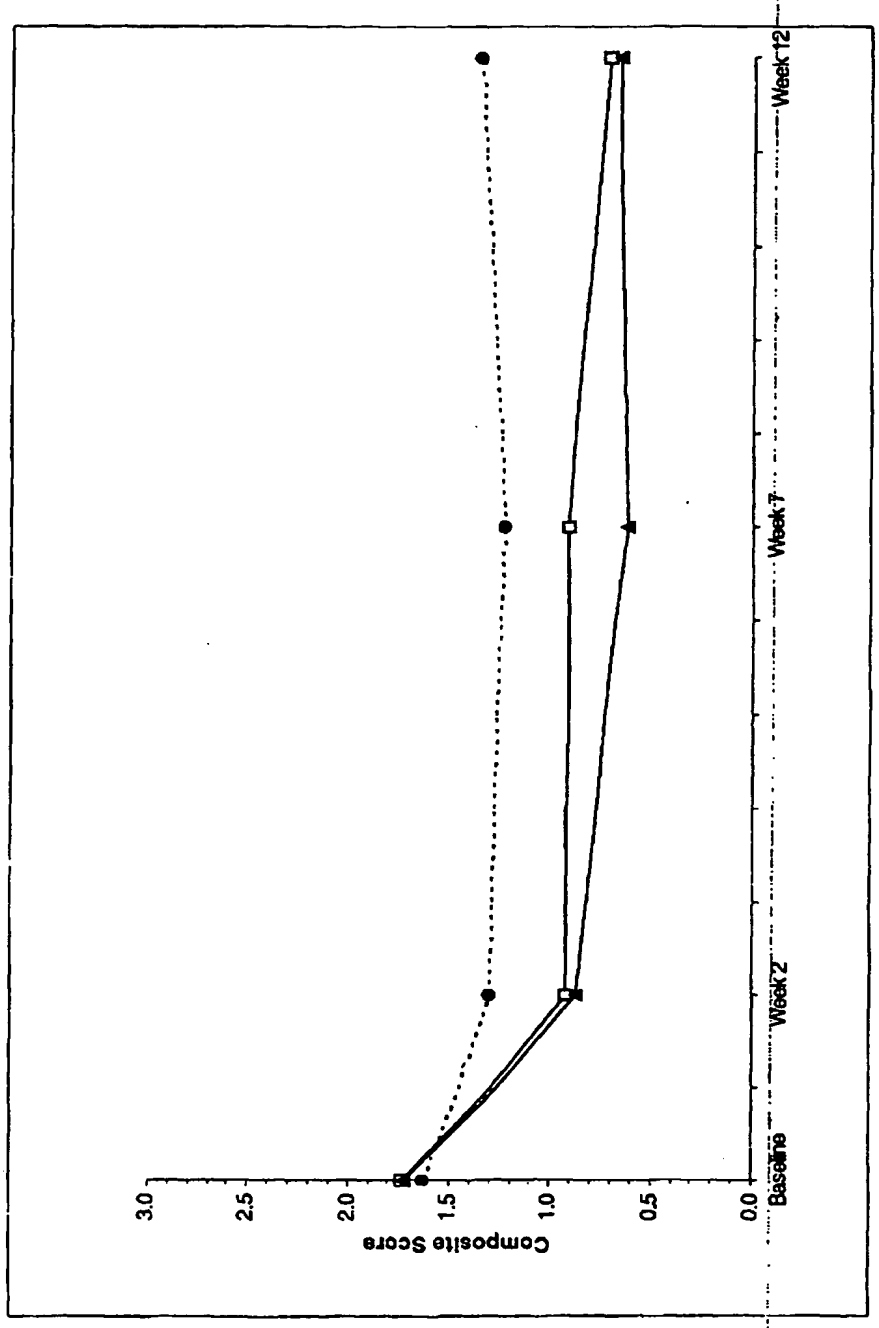
Figure 6. Percentages of superficial vaginal and urethral cells – subjects who had superficial vaginal and urethral cell assessments at Weeks 0 and 12

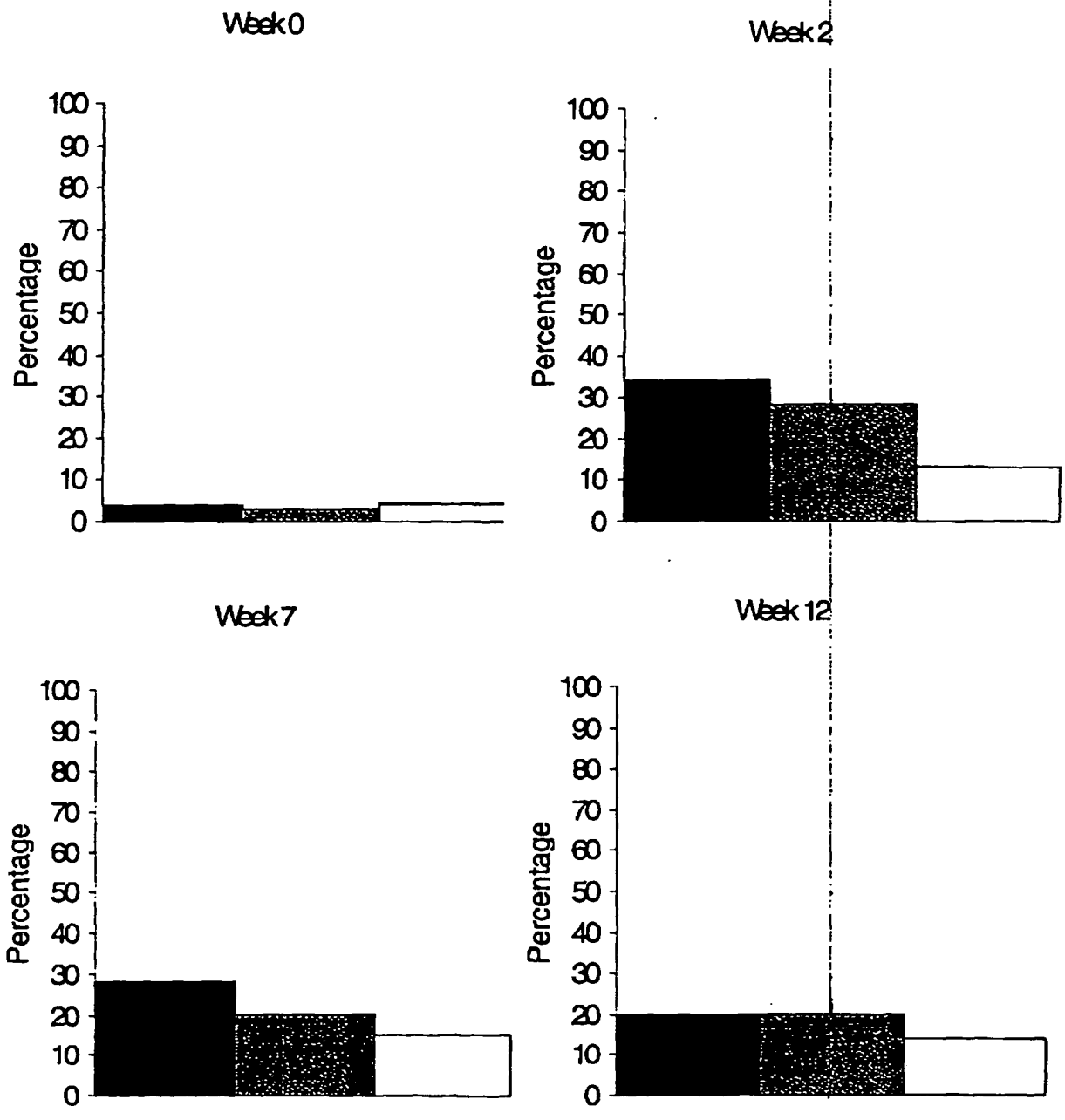
(a) 17-β E2 25 μg

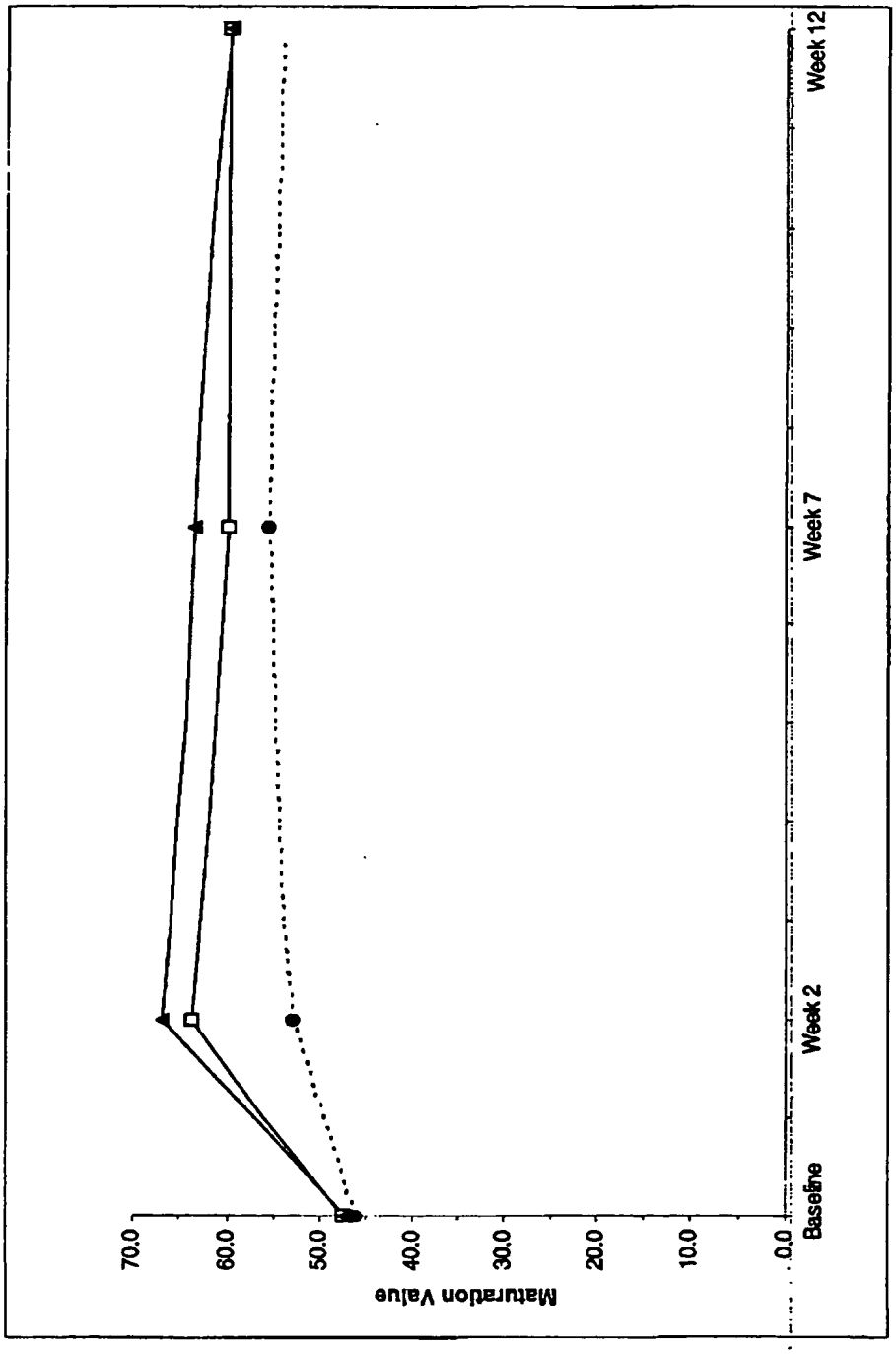
(b) 17-β E2 10 μg

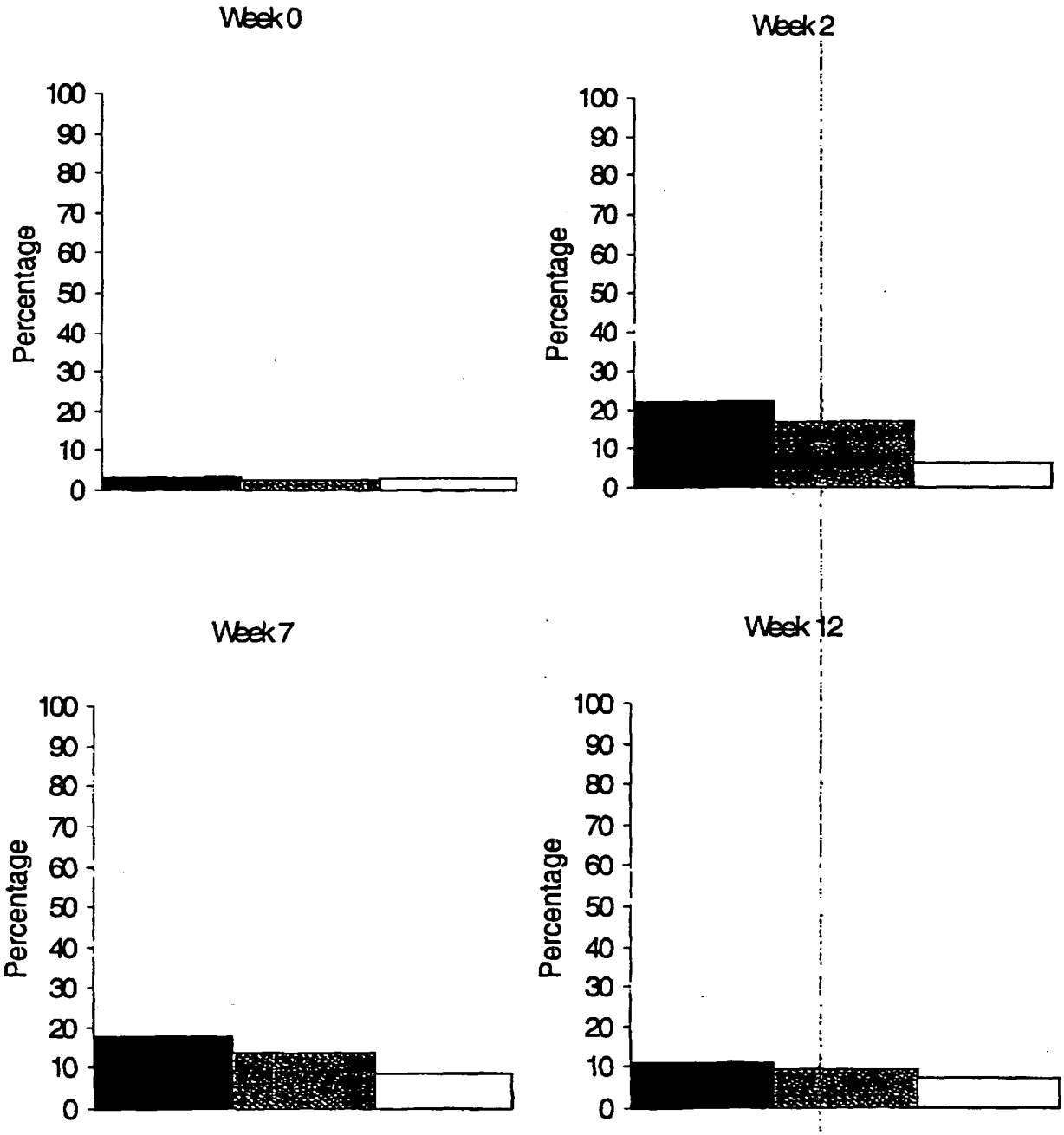
(c) Placebo











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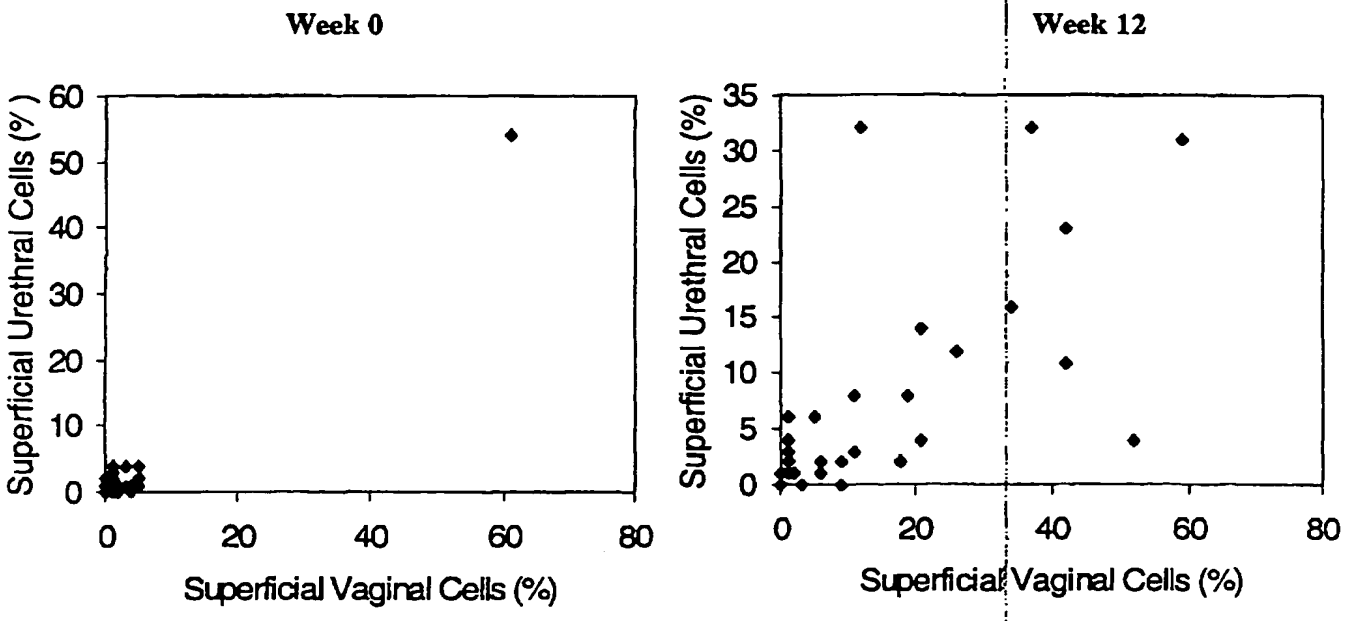

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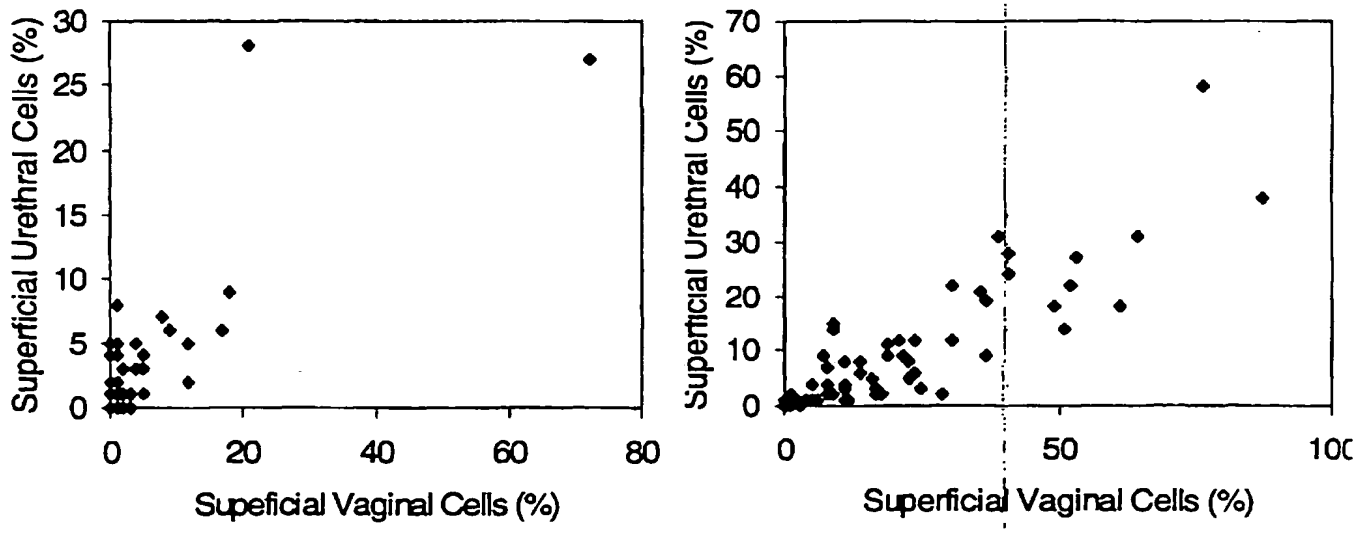

(c)